Amendment to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A method for screening for an agent that modulates BMP-mediated signaling, comprising ~~the steps of~~:

(a) contacting

(i) a first polypeptide comprising a HECT E3 ubiquitin ligase WW domain; SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, or a variant thereof in which the ability of the polypeptide to bind to a Smad protein is not substantially diminished relative to the HECT E3 ubiquitin ligase;

(ii) a second polypeptide comprising a Smad PY motif; SEQ ID NO:14, 15, 16, 17, 20, 21, 22, 23, 24, or 25, or a variant thereof in which the ability of the polypeptide to bind to an E3 ubiquitin ligase is not substantially diminished relative to a native Smad protein comprising the PY motif; and

(iii) a candidate agent;

under conditions that permit a detectable level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent; and

(b) ~~determining a level of binding of the first polypeptide to the second polypeptide; and~~ ~~(c)~~ comparing the level of binding of the first polypeptide to the second polypeptide in the presence of the candidate agent to a control level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent, and therefrom determining whether the candidate agent modulates BMP-mediated signaling.

2. (Currently amended) The ~~A~~ method according to claim 1, wherein the HECT E3 ~~upiquitin~~ ubiquitin ligase WW domain comprises the sequence:

Gly-Pro-Leu-Pro-Xaa-Gly-Trp-Glu-Xaa-Xaa-Xaa-Taa-Taa-Taa-Gly-Taa-Xaa-Tyr-Tyr-Haa-Xaa-His-Asn-Thr-Taa-Thr-Thr-Taa-Trp-Xaa-Taa-Pro-Taa (SEQ ID NO:2);

~~GPLPXGWEX$_3$tttGtXYYhXHNTtTTtWXtPt (SEQ ID NO:2)~~

wherein each Taa ~~each t~~ is an independently selected polar amino acid residue, Haa is ~~h is~~ a hydrophobic residue and each Xaa ~~each X~~ is an independently selected amino acid residue.

3. (Currently amended) The ~~A~~ method according to claim 1, wherein the Smad PY motif comprises the sequence Ser/Thr-Pro-Pro-Pro-Pro/Ala/Gly-Tyr (SEQ ID NO:15), wherein Ser/Thr is an amino acid residue that is serine or threonine and Pro/Ala/Gly is an amino acid residue that is selected from the group consisting of proline, alanine and glycine.

4. (Currently amended) The ~~A~~ method according to claim 3, wherein the Smad PY motif comprises the sequence Thr-Pro-Pro-Ala-Tyr ~~TPPPAY~~ (SEQ ID NO:16) or Thr-Pro-Pro-Pro-Gly-Tyr ~~TPPPGY~~ (SEQ ID NO:18).

5. (Currently amended) The ~~A~~ method according to claim 1, wherein the candidate agent is a small molecule within a combinatorial library.

6. (Currently amended) The ~~A~~ method according to claim 1, wherein the first polypeptide is immobilized on a solid support and the second polypeptide comprises a tag.

7. (Currently amended) The ~~A~~ method according to claim 1, wherein the second polypeptide is immobilized on a solid support and the first polypeptide comprises a tag.

8. (Currently amended) The ~~A~~ method according to claim 6 or claim 7, wherein the tag is biotin or a radioactive group.

9. (Currently amended) The ~~A~~ method according to claim 1, wherein the level of binding is determined via a two-antibody sandwich assay.

10. (Currently amended) The ~~A~~ method according to claim 1, wherein the level of binding is determined via a competitive assay.

Claims 11-54 - Cancelled.

~~54.~~ 55. (Currently amended) The ~~A~~ method according to claim 2, wherein ~~each t~~ each Taa is selected from the amino acid residue group consisting of Ser, His, Pro, Asp, Glu, Thr, and Tyr ~~S, H, P, D, E, T and Y~~.

~~55.~~ 56. (Currently amended) The ~~A~~ method according to claim 2, wherein ~~each h~~ each Haa is selected from the hydrophobic residue group consisting of Ile, Val, Leu, and Met ~~I, V, L and M~~.

57. The method of claim 1, wherein:

(i) when the level of binding of the first polypeptide to the second polypeptide is increased as compared to the control level, the agent decreases BMP-mediated signaling, or

(ii) when the level of binding of the first polypeptide to the second polypeptide is decreased as compared to the control level, the agent increases BMP-mediated signaling.

58. (New) The method of claim 1, wherein said determining whether the candidate agent modulates BMP-mediated signaling further comprises the step of measuring or otherwise determining the level of Smad ubiquitination in the presence of the agent as compared to in the absence of the agent, wherein:

(i) an increase in Smad ubiquitination indicates the agent decreases BMP-mediated signaling, or

(ii) a decrease in Smad ubiquitination indicates the agent increases BMP-mediated signaling.

59. (New) The method of claim 1, wherein said determining whether the candidate agent modulates BMP-mediated signaling further comprises the step of measuring or otherwise determining the level of Smad protein in the presence of the agent as compared to in the absence of the agent, wherein:

(i) an increase in Smad protein indicates the agent increases BMP-mediated signaling, and

(ii) a decrease in Smad protein indicates the agent decreases BMP-mediated signaling.